Editorial

Perspectives in small cell lung cancer: is something moving?

Lucio Crinò, Angelo Delmonte

Department of Medical Oncology, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori, Meldola, Italy

Correspondence to: Lucio Crinò. Department of Medical Oncology, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori, Via Maroncelli 40, 47014 Meldola, Italy. Email: lucio.crino@irst.emr.it.

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Small cell lung cancer (SCLC) represents one of the major challenges of the modern oncology. Its very aggressive behavior with rapid growth, early metastasis and rapid development of resistances to treatments, despite an early response, shorten the life expectances of patients affected by the extensive stage disease to approximately 10–12 months from the diagnosis (1) with a 2-year overall survival (OS) rate of 5% (2,3). In effect the first line of treatment, consistent in a doublet of a platinum-based agent and etoposide, obtain an overall response rate (ORR) of approximately 70% (4) that can be partly improved by adding, when possible, prophylactic cranial and thoracic radiation (5,6). However responses to first line have a very limited duration that rarely exceed 6 months (4). At recurrence therapeutic strategies are limited to few options that essentially haven't changed since 1996 when topotecan was defined as the standard second line. The ORR obtained by topotecan is in the 15% to 24% range, median time to progression (TTP) is 13.3 weeks and median survival time is 25 weeks. These results have been relevant at that time because for the first time single-agent chemotherapy has shown in this setting similar activity to combination chemotherapy with less toxicity (7). However many attempts of improvement in the last 20 years have been conducted with several chemotherapeutic agents, such as irinotecan, gemcitabine or pemetrexed, with unconvincing results (8). Only amrubicin, a fully synthetic 9 amino anthracyclin, pro-drug of amrubicinol, has shown in several phase II and III trial hints of major activity than that of topotecan. In fact in the ACT-1 phase III trial amrubicin has shown an ORR of 31.1% *vs.* 16.9% in the topotecan control arm (odds ratio 2.223, P<0.0001). However no differences have been seen in term of progression free survival (PFS) and OS, even if in the experimental arm less frequent grade 3–4 hematologic toxicities have been seen (9). On the basis of these data amrubicin has been registered and is available in second line treatment of SCLC in Japan.

The improvement of results in several oncologic fields by introducing the translational approach has increased expectations also in SCLC. Recent publications has proposed a new classification of SCLC in 3 major subgroups according to the expression of the neuronal basic helix-loop-helix transcription factors *achaete-scute homologue 1* (*ASCL1*), involved in the neuroendocrine characterization, and the *neurogenic differentiation factor 1* (*NEUROD1*). The so called "classic type" shows expression of *ASCL1*, the "variant type" expresses *NEUROD1* and the third type is negative for both the two previous biomarkers. In term of gene profiling these subgroups are clearly distinct but at present their meaning in term of prognosis and prediction of response to treatment are unclear (10). Many pathways have been studied, such as for example *EGFR*, *RET*, *mTORC1* (11) and others are under evaluations, such as *PARP*, *EZH2*, *WEE1* and epigenetic alterations (10). However no driver mutations have been identified and the heterogeneity at the basis of SCLC can be the reason of the failure of clinical trials with targeted therapies seen until now (11). Promising results are emerging by the increasing knowledge of the Notch

pathway of which an involvement in SCLC oncogenesis has been shown (12). In fact Notch acts as a tumor suppressor gene in neuroendocrine tumors including SCLC. In this context the *delta-like protein 3* (*DLL3*), a member of the Notch receptor ligand family, is able to inhibit the tumor suppressor activity of Notch itself. Given that *DLL3* is upregulated in high-grade neuroendocrine tumors, such as SCLC, acting as oncogenic driver, it has become a potential target for therapies (10). The drug with the most advanced state of development in this field is rovalpituzumab tesirine which is a *DLL3*-targeted antibody conjugated consisting of the *DLL3*-specific IgG1 monoclonal antibody SC16, the DNA cross-linking agent SC-DR002 (D6.5) and a protease-cleavable linker. This is a first-in-human, first-in-class drug of which the results of a phase 1 trial in SCLC and large cell neuroendocrine carcinoma have been recently published (13). Among the overall 65 pretreated patients evaluable for response 11 (17%) had an objective response and 35 (54%) a stable disease with a disease control in 46 patients (71%). Of 29 patients with high level of expression of *DLL3* (>50%), 10 (35%) had a confirmed objective response and 26 (90%) had a disease control. Of 10 patients with low expression of *DLL3* (<50%), 6 (60%) had a disease control. Progression-free survival, median OS and 1-year OS were 4.5 months, 5.8 months an 18% in the *DLL3*-high patients and 2.3 months, 2.7 months and 0% in the *DLL3*-low group respectively. The safety profile was manageable even if not negligible. In fact grade 3 toxicities were thrombocytopenia in 11% of patients, pleural effusion in 8% and increased lipase in 7%. To date these results are under further evaluations in several clinical trials in various settings fos extensive SCLC.

Across multiple tumor types recent exciting results have been obtained by acting against the ability of cancer to escape from immune surveillance. Immune-checkpoint inhibitors against cytotoxic *T-lymphocyte-associated protein 4* (*CTLA-4*), programmed cell death protein 1 (PD-1) and its ligand PD-L1, may be a new potential strategy also for extensive-stage SCLC which is characterized by a high mutational burden and a consequent large number of potential tumor-specific antigens (14,15), features that apparently may favor the activity of these drugs. Many trials are ongoing but only limited results have been published until now. Different schedules of the anti-PD-1 nivolumab combined with the anti-*CTLA-4* Ipilimumab were evaluated in the phase 1/2 trial Checkmate 032: nivolumab 3 mg/kg every 2 weeks or nivolumab and ipilimumab (1 and 1 mg/kg, 1 and 3 mg/kg, 3 and 1 mg/kg) every 3 weeks for 4 cycles followed by nivolumab 3 mg/kg every 2 weeks. A total of 216 patients have been enrolled, divided into the 4 arms. In the nivolumab arm confirmed objective responses have been seen in 10% patients while in the combination arms in 19% to 23% of patients. Responses were independent from the status of sensibility to platinum and not related to PD-L1 expression. Median duration of response was not reached in the nivolumab arms and in the combo arms ranged from 4.4 to 9.6 months. One-year PFS and OS ranged from 11% and 33% in Nivolumab arm to 19% and 43% for the nivolumab 1 mg/kg and ipilimumab 3 mg/kg cohort, respectively. From the safety point of view no major differences have been seen from other trials with this combination, with grade 3–4 events (increased lipase and diarrhoea) in 13% of patients in the nivolumab arm and in 19% to 30% of patients in the combo arms. Three patients died due to treatment-related adverse events, two in the nivolumab 1 mg/kg and ipilimumab 3 mg/kg (myasthenia gravis and worsening of renal failure) and one in nivolumab 3 mg/kg and ipilimumab 1 mg/kg group (pneumonitis) (16). Another trial, a randomized double-blind phase III trial in extensive-stage SCLC, has evaluated standard chemotherapy with platinum and etoposide combined with ipilimumab 10 mg/kg or placebo every 3 weeks in a phased induction schedule (chemotherapy in cycles one to four; ipilimumab beginning in cycle three up to cycle six) followed by maintenance with ipilimumab or placebo. Among 954 patients evaluable, median PFS and OS were 4.6 and 11 months in the chemotherapy plus ipilimumab arm and 4.4 and 10.9 in the control arm, respectively. These disappointing results have been worsened by the fact that, even if the rates and severity of adverse events have been similar in the two arms, the treatment-related discontinuation rate was higher in the experimental arm (18% *vs.* 2% in the control arm), with 5 treatment-related deaths in the chemotherapy plus ipilimumab arm and 2 in the chemotherapy plus placebo group (17).

Recently Ott and colleagues (18) have added new information to the landscape of immunotherapy publishing in Journal Clinical Oncology the results of the Keynote-028 study, a phase Ib study cohort of extensive SCLC performed in 1 year at four institutions in USA, Europe and Asia. This work reports the activity and safety of Pembrolizumab, an anti-PD-1 checkpoint inhibitor, in a phase 1b multi cohort experience explorating data relative to a highly selected extensive SCLC population with expression of PD-L1 ≥1% of tumor and inflammatory cells, good performance status (<2) despite several lines of treatment (from 1 to more than

3 previous lines). Among 163 patients evaluated 46 (31.7%) expressed PD-L1 ≥1% and only 24 of them received the treatment. The ORR was 33% with median duration of response, PFS and OS of 19.4, 1.9 and 9.7 months. The 6- and 12-month OS rates were 66% and 37.7%, respectively. Safety profile showed 33.3% of grade 3–5 adverse events with only 8% related to drug (increased values of bilirubin, asthenia and colitis/intestinal ischemia) with one resulting in death. These results are very promising showing an ORR of 33% with early onset and long lasting duration, with a mild toxicity which compare favorably with the known efficacy-toxicity profile of topotecan and deserve further evaluation in phase II–III well designed trials. This experience has a number of limitations and positive findings. First of all immunotherapy and in specific Pembrolizumab appears to be potential alternative strategy to chemotherapy in second line treatment for extensive SCLC. In this sense, this study is opening a discussion which can be useful for the future developments. The number of patients is limited, only 24, and highly selected from a screened population of 163 extensive SCLC on the basis of a good performance status and PD-L1 expression superior to 1%. This group of patients can't be considered representative of the usual resistant or relapsing SCLC population who usually doesn't maintain an adequate performance status after the first line of chemotherapy. Moreover patients in this setting presents brain metastasis in a larger percentage than the 12% reported in this study which has excluded those who had unstable brain metastasis. PD-L1 couldn't be the best biomarker to select patients in this setting which generally are heavy smokers, with a high neoantigens presence and a possible relevant mutational tumor burden which has to be explored in SCLC similarly to what is happening in non-small cell lung cancer. Toxicity profile has been reported as mild but among 24 treated patients, it has occurred a toxic death because of mesenteric ischemia and colitis which has been already described as a severe side effect related to immune checkpoints treatment. Pembrolizumab related adverse events were seen in 16 (66.7%) of 24 patients mostly evaluated as grade 1 non requiring therapy discontinuation.

Putting together all these data, reasons for more hopes than those in the past are arising even if a deeper knowledge of the activity of all these new compound is required. However the prospective to have new possible therapeutic opportunities after years of immobility in SCLC can give to all oncologic community strong motivations for a hard work in this field. It seems clear, in reviewing this experience, that a careful selection of patients should be important to clarify the role of immunotherapy and to get a significant improvement in the outcome of extensively pretreated SCLC patients as well as the identification of specific biomarkers to address the best population for immunotherapy.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Rudin CM, Ismaila N, Hann CL, et al. Treatment of Small-Cell Lung Cancer: American Society of Clinical Oncology Endorsement of the American College of Chest Physicians Guideline. J Clin Oncol 2015;33:4106-11.
2. Alvarado-Luna G, Morales-Espinosa D. Treatment for small cell lung cancer, where are we now?-a review. Transl Lung Cancer Res 2016;5:26-38.
3. Hurwitz JL, McCoy F, Scullin P, et al. New advances in the second-line treatment of small cell lung cancer. Oncologist 2009;14:986-94.
4. Rossi A, Di Maio M, Chiodini P, et al. Carboplatin- or cisplatin-based chemotherapy in first-line treatment of small-cell lung cancer: the COCIS meta-analysis of individual patient data. J Clin Oncol 2012;30:1692-8.
5. Slotman BJ, van Tinteren H, Praag JO, et al. Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. Lancet 2015;385:36-42.
6. Slotman B, Faivre-Finn C, Kramer G, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. N Engl J Med 2007;357:664-72.
7. von Pawel J, Schiller JH, Shepherd FA, et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. J Clin Oncol 1999;17:658-67.
8. Asai N, Ohkuni Y, Kaneko N, et al. Relapsed small cell lung cancer: treatment options and latest developments. Ther Adv Med Oncol 2014;6:69-82.
9. Jotte R, Conkling P, Reynolds C, et al. Randomized phase II trial of single-agent amrubicin or topotecan as second-line treatment in patients with small-cell lung cancer

sensitive to first-line platinum-based chemotherapy. J Clin Oncol 2011;29:287-93.
10. Sabari JK, Lok BH, Laird JH, et al. Unravelling the biology of SCLC: implications for therapy. Nat Rev Clin Oncol 2017;14:549-61.
11. Koinis F, Kotsakis A, Georgoulias V. Small cell lung cancer (SCLC): no treatment advances in recent years. Transl Lung Cancer Res 2016;5:39-50.
12. George J, Lim JS, Jang SJ, et al. Comprehensive genomic profiles of small cell lung cancer. Nature 2015;524:47-53.
13. Rudin CM, Pietanza MC, Bauer TM, et al. Rovalpituzumab tesirine, a DLL3-targeted antibody-drug conjugate, in recurrent small-cell lung cancer: a first-in-human, first-in-class, open-label, phase 1 study. Lancet Oncol 2017;18:42-51.
14. Khalil DN, Smith EL, Brentjens RJ, et al. The future of cancer treatment: immunomodulation, CARs and combination immunotherapy. Nat Rev Clin Oncol 2016;13:394.
15. Sharma P, Allison JP. The future of immune checkpoint therapy. Science 2015;348:56-61.
16. Antonia SJ, López-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. Lancet Oncol 2016;17:883-95.
17. Reck M, Luft A, Szczesna A, et al. Phase III Randomized Trial of Ipilimumab Plus Etoposide and Platinum Versus Placebo Plus Etoposide and Platinum in Extensive-Stage Small-Cell Lung Cancer. J Clin Oncol 2016;34:3740-8.
18. Ott PA, Elez E, Hiret S, et al. Pembrolizumab in Patients With Extensive-Stage Small-Cell Lung Cancer: Results From the Phase Ib KEYNOTE-028 Study. J Clin Oncol 2017;35:3823-9.

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